

AMENDMENTS TO THE SPECIFICATION

Please replace the paragraph starting at page 4, line 26, with the following paragraph:

The present invention provides materials and methods for treating a variety of tumors including noncentral nervous system tumors and tumors of the central nervous system origin. The treatment methods involve infecting target tumors with genetically modified herpes simplex virus wherein the modification comprises a modification of an internal inverted repeat region of the herpes simplex virus genome. In a preferred embodiment the modification of the herpes simplex virus genome comprises the deletion of one copy of the internal repeat sequence of the viral gene which region comprises one copy each of ICP0, IPC4, ORFO, ORFP and γ_1 34.5 genes. The herpes simplex viruses useful in the practice of the invention are attenuated with respect to the wild-type herpes simplex viruses but are more replication competent than viruses having both copies of the inverted repeat region modified (to render the region incapable of expressing an actual gene product of any one of the various genes) or deleted. Viruses useful in the practice of the present invention may have additional alterations in their genome that may include insertion of expressible non-natural protein encoding sequences under the control of herpes simplex virus promoters that in turn permits the sequence to be regulated as an α , β or γ class of herpes simplex virus genes that are well known in the art. [See, *e.g. Fundamental Virology, Second Edition*, Field *et al.* (eds.) Chapters 33-34, Raven Press Ltd., New York (1991) incorporated herein by reference.]

Viruses lacking internal repeated can be further attenuated if necessary by the deletion of one or more of the 47 46 genes found dispensable for viral replication in culture, which include γ_1 34.5, ORFP, ORFO, α 0, U_L2, U_L3, U_L4, U_L10, U_L11, U_L12, U_L12.5, U_L13, U_L16, U_L20, U_L21, U_L23, U_L24, U_L39, U_L40, U_L41, U_L43, U_L43.5, U_L44, U_L45, U_L46, U_L47, U_L50, U_L51, U_L53, U_L55, U_L56, α 22, U_S1.5, U_S2, U_S3, U_S4, U_S5, U_S7, U_S8, U_S8.5, U_S9, U_S10, U_S11, α 47, Ori_STU, and LATU. [Roizman, *Proc. Natl. Acad. Sci. (USA)* (1996)]. Among the genes suitable for deletion to decrease further virulence are the U_L16, U_L40, U_L41, U_L55, U_L56, α 22, U_S4, U_S8, and U_S11 genes. Deletion of virtually any one of the "dispensable" genes will reduce virulence by a factor ranging from twofold to several logs. In addition, candidate viruses lacking the internal inverted repeats may be further altered by the addition of cytokines, as well as enzymes that activate prodrugs.